Research of the Method for Assessing Facial Phenotypic Features from 2D Images in Medical Genetics

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Abstract: The paper proposes and investigates the phenotypic facial features recognition method based on facial points coordinates on a reconstructed 3D facial image. The accuracy of the determination of phenotypic features was investigated. The method recognizes phenotypic features with an accuracy of 84 % to 100 %. The method has been tested on open and own databases of facial images of patients with hereditary diseases. A criterion for the forming a risk group for Williams syndrome was proposed based on the summation of the absolute values of z-scores of phenotypic features. On own database, the criterion provides an AUC value of 0.922 for the separation of the Williams syndrome and the norm.

1 INTRODUCTION

According to the World Health Organization, almost 8 % of the population suffers from hereditary diseases; more than 7000 such diseases are known (Hart and Hart, 2009). Genetic pathology accounts for a significant portion of childhood morbidity, mortality, and disability.

Despite the growing importance of molecular genetic methods and an increase in their efficiency in diagnosing of hereditary diseases, the analysis of phenotypic manifestations remains extremely important since it allows one to determine a clinical hypothesis and correctly interpret the results of laboratory studies. The description of the face and head is critical since 30 % to 40 % of genetic diseases are associated with changes in the anatomical structure of the craniofacial region (Hart and Hart, 2009).

Unlike congenital malformations, congenital morphogenetic variants (minor physical anomalies) do not disrupt organ functions, and their differentiation from normal variants is often problematic. Nevertheless, in the scientific and medical literature, it has been shown that both the number of revealed phenotypic traits corresponding to congenital morphogenetic variants and their certain combinations have diagnostic significance (Antonov et al., 2011; Meleshkina et al., 2015).

Therefore, recognizing facial phenotypic features is essential, particularly for forming of a diagnostic criterion for the presence of a hereditary disease.

There are works on the recognition of several syndromes based on facial 2D images (for example, Gurovich et al., 2019), but in the space of features that do not coincide with the phenotypic features used in anthropometry. This circumstance complicates the interpretation of the results obtained.

In (Kumov et al., 2019), a method was developed for assessing phenotypic features from a 2D image using a standard set of 68 points. Statistically significant differences are shown in these features between the Noonan and Williams syndromes.

Further improvement of methods for assessing phenotypic features of the face and head based on automated measurements is required. This will reduce the subjectivity of recognizing facial phenotypic features in clinical practice. The development of a method for analyzing facial images of patients with hereditary diseases based on recognizing phenotypic features will make the results more interpretable.

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2 RESEARCH

A review of the phenotypic facial features is carried out, followed by a study of the accuracy of recognition of phenotypic facial features using simulation.

2.1 Method for Assessing Facial Phenotypic Features

One of the complete standardized descriptions of the phenotypes of genetic diseases was developed as part of the Human Phenotype Ontology (HPO) project (Robinson et al., 2008). Currently, the HPO dictionary is widely used in projects aimed at describing the phenotypes of patients and understanding the molecular mechanisms underlying their diseases, as well as for indexing and annotating information in databases on human genetics (Online Mendelian Inheritance in Man, Orphanet, GWAS Central, ClinVar) and in various electronic health records systems.

Several phenotypic traits presented in the HPO dictionary are defined in terms of distances between given anthropometric points. Automation of the assessment of such features implies both the automatic localization of the corresponding anthropometric points and the determination of the distance between them, taking into account the scale of the image and the comparison of the obtained value with the norm, which significantly depends on race, age and gender. Localization of the facial points in the image, based on the use of special software tools, is widely used in medical problems, in particular, for the diagnosis of Parkinson's disease (Moshkova et al., 2020, 2021).

Complete statistical data on anthropometric distances characterizing the structure of the craniofacial region were collected as part of the FaceBase project (Hochheiser et al., 2011). The data contains information on the average values of the norm and standard deviations for 34 distances for people of the European population, taking into account gender and age (from 3 to 40 years). The distances were determined in accordance with the system of anthropometric measurements proposed by L. Farkas (Farkas, 1994).

In this work, from a variety of phenotypic traits, a set was selected that includes 32 linear distances from Facebase, which can be estimated from the results of 3D face reconstruction (Deng et al., 2019). This set includes 13 distances used in the HPO dictionary.

Distances between points calculated from the face image should consider the image scale. For this, we used the normalization to the average of all 32 distances. After normalization, each distance is compared to the normal range for the corresponding group to calculate a z-score.

Based on the calculated features, a description of the face is obtained in terms of the standardized vocabulary of phenotypic anomalies of the HPO project. For each characteristic, three ranges of values are obtained. If the absolute value of the z-score does not exceed 2, then the corresponding phenotypic trait is assigned the value "normal". If the z-score goes beyond the normal range from below, then the value "reduced" is assigned, for example, depending on the attribute, "Narrow", "Thin", "Short", "Hypotelorism". Finally, if the z-score is outside the upper limit of the norm, then a value of "increased" ("Thick", "Long", "Broad", "Wide" or "Hypertelorism") is assigned. These estimates are constructed both for 13 features used in the HPO dictionary and, by analogy, for all other features.

The diagram of the developed method for assessing facial phenotypic features from a 2D image is shown in Figure 1.

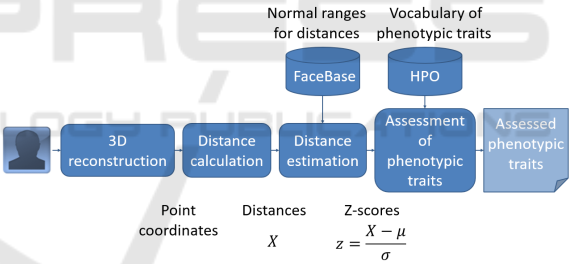


Figure 1: Diagram of the method for assessing facial phenotypic features from an image.

2.2 Recognition Accuracy of Facial Phenotypic Features

The recognition accuracy of facial phenotypic features was assessed using the following computational experiment.

For images of healthy subjects of different gender and age (from 6 to 16 years) from the database (Dalrymple et al., 2013), a 3D reconstruction was performed, the result of which was taken as a reference 3D image of the face, which was used to determine the actual values of phenotypic traits. The stages of face image preprocessing, 3D face reconstruction, and point determination are similar to those in (Kumov and Samorodov, 2020). For face detection, the classical

Viola-Jones method was used, but it is also possible to use more advanced solutions based, in particular, on neural network models (Aung et al., 2021).

In total, 80 reference 3D images were created, according to the number of images of different individuals in the database.

According to the phenotypic traits of these reference 3D images, the mean values and standard deviations (regardless of gender and age) were calculated and used to obtain z-scores. Another approach used the parameters of statistical distributions of distances between points for healthy people, taken from the FaceBase project, taking into account gender and age.

Each reference 3D image was projected onto the frontal plane with the formation of 2D images of faces, to which were applied the methods of automatic localization of points (without manual correction), 3D reconstruction, and assessment of phenotypic traits using the reconstructed coordinates of points with the estimation of z-scores and classification of the phenotypic trait on three classes (3 ranges of values). If the resulting feature class differed from the actual class in the reference 3D image, the feature recognition was considered as an error.

The modeling diagram is shown in Figure 2.

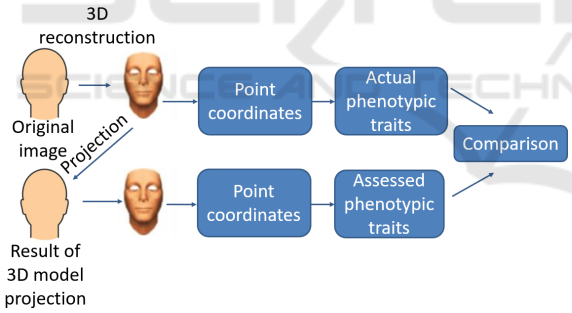


Figure 2: Modeling diagram.

The results of the computational experiment are shown in Table 1.

The minimum accuracy in assessing features without regard to age and gender is 88 %, the maximum accuracy is 99 %. Not less than 27 features were recognized with an accuracy of 90 %, 12 features with 95 %, and 2 features with 97 %.

The histogram of the number of feature recognition errors for 80 projections compared to the reference 3D images without considering age and gender is shown in Figure 3. For nine images (11.2 % of the total number of images), the number of errors is five or more.

Table 1: Recognition accuracy of facial phenotypic features.

№	Feature	Accuracy with / without regard to gender and age, %		№	Feature	Accuracy with / without regard to gender and age, %	
		without	with			without	with
1	Minimum Frontal Width	95	100	17	Palpebral Fissure Length Left	95	85
2	Maximum Facial Width	95	100	18	Nasal Width	95	100
3	Mandibular Width	94	84	19	Subnasal Width	91	89
4	Cranial Base Width	94	100	20	Nasal Protrusion	89	92
5	Upper Facial Depth Right	89	96	21	Nasal Ala Length Right	90	98
6	Upper Facial Depth Left	91	99	22	Nasal Ala Length Left	89	100
7	Middle Facial Depth Right	90	100	23	Nasal Height	98	100
8	Middle Facial Depth Left	94	100	24	Nasal Bridge Length	89	98
9	Lower Facial Depth Right	95	99	25	Labial Fissure Width	94	99
10	Lower Facial Depth Left	94	99	26	Philtrum Width	95	100
11	Morphological Facial Height	88	100	27	Philtrum Length	96	100
12	Upper Facial Height	92	99	28	Upper Lip Height	92	100
13	Lower Facial Height	94	99	29	Lower Lip Height	92	99
14	Intercanthal Width	95	90	30	Upper Vermilion Height	95	100
15	Outercanthal Width	99	100	31	Lower Vermilion Height	95	99
16	Palpebral Fissure Length Right	94	85	32	Cutaneous Lower Lip Height	92	100

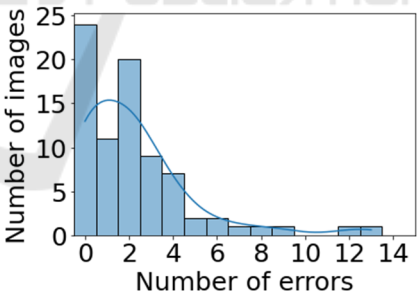
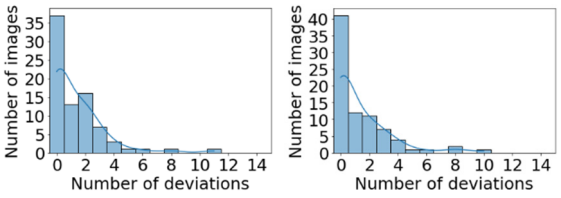


Figure 3: Histogram of the number of feature recognition errors for 80 images without regard to age and gender.

Histograms of the number of feature deviations for reference 3D images and projections without regard to age and gender are shown in Figure 4. For approximately half of the considered images (37 out of 80 – in references, 41 out of 80 – in projections) the number of feature deviations from the norm is zero. The number of deviations of features in references does not exceed four for 95 % of images (93.7 % – in projections).



a) b)

Figure 4: Histograms of the number of feature deviations for 80 images (a – in references, b – in projections, assessment of 32 features without regard to age and gender).

The minimum accuracy in assessing features considering age and gender is 84 %, the maximum accuracy is 100 %. Accounting for age and gender improves recognition accuracy. The number of features recognized with an accuracy not less than 90 % is 28, 95 % – 26, and 97 % – 25.

The histogram of the number of feature recognition errors for 80 projections compared to the reference 3D images, taking into account age and gender, is shown in Figure 5. The maximum number of errors is three (this number of errors is observed in 5 images out of 80).

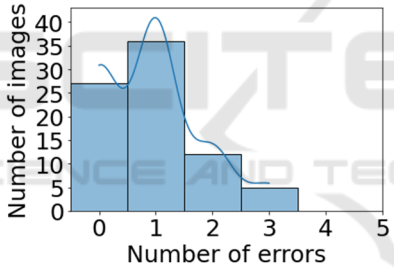
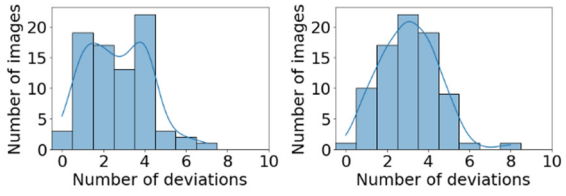


Figure 5: Histogram of the number of feature recognition errors for 80 images considering age and gender.

Histograms of the number of feature deviations for references and projections, taking into account age and gender, are shown in Figure 6. For most of the considered images, the number of deviations of features from the norm does not exceed five (for 96.2 % of images – in references, for 97.5 % – in projections).



a) b)

Figure 6: Histograms of the number of feature deviations for 80 images (a – in references, b – in projections, assessment of 32 features, taking into account age and gender).

The accuracy of the assessment of 13 features of HPO, taking into account age and gender, is shown in Table 2.

Table 2: Recognition accuracy of 13 HPO features, taking into account age and gender.

№	HPO features	Values of HPO features	Accuracy, %
1	Face	Broad, Normal, Narrow	100
2	Face	Long, Normal, Short	100
3	Distance between eyes	Hypertelorism, Normal, Hypotelorism	90
4	Palpebral Fissure Right	Long, Normal, Short	85
5	Palpebral Fissure Left	Long, Normal, Short	85
6	Nose	Wide, Normal, Narrow	100
7	Nose	Normal, Prominent	92
8	Nose	Long, Normal, Short	100
9	Mouth	Wide, Normal, Narrow	99
10	Philtrum	Broad, Normal, Narrow	100
11	Philtrum	Long, Normal, Short	100
12	Upper Lip Vermilion	Thick, Normal, Thin	100
13	Lower Lip Vermilion	Thick, Normal, Thin	99

The minimum accuracy in assessing features considering age and gender is 85 %, the maximum accuracy is 100 %. The number of features recognized with an accuracy not less than 90 % is 11, 95 % – 9, and 97 % – 9.

The histogram of the number of feature recognition errors for projections compared to the reference 3D images, taking into account age and gender, is shown in Figure 7. The maximum number of errors is three (this number of errors is observed in 1 image out of 80).

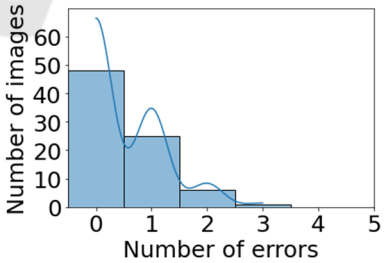
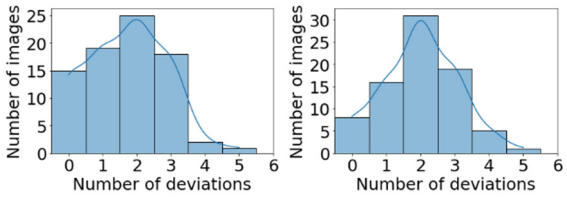


Figure 7: Histogram of the number of feature recognition errors for 80 images (estimation of 13 HPO features, taking into account age and gender).

Histograms of the number of HPO feature deviations for references and projections, taking into account age and gender are shown in Figure 8. For most images, the number of deviations of features from the norm does not exceed three (for 96.2 % of images – in references, for 92.5 % – in projections).



a) b)

Figure 8: Histograms of the number of feature deviations for 80 images (a – in references, b – in projections, assessment of 13 HPO features, taking into account age and gender).

When gender and age are taken into account, the number of features with recognition accuracy above 95 % and 97 % significantly increases.

Thus, high accuracy of phenotypic features recognition and the possibility of automatic formation of a phenotypic face portrait have been demonstrated.

2.3 Study of the Distributions of Deviations in the Group of the Norm and Available Pathology

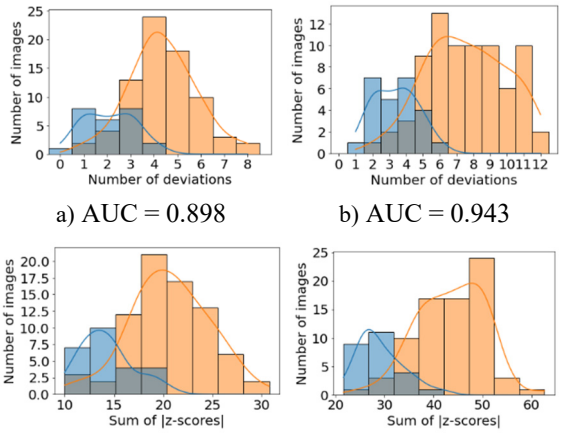
2.3.1 Open Database

The developed method for assessing phenotypic features was tested on an open verified database of patients with hereditary diseases (Ferry et al., 2014). Unlike (Kumov, 2020), where a pre-trained neural network model based on the VGG16 architecture (which is widely used in other fields, in particular, in the analysis of geographical information (Tun et al., 2021) was applied in the method of recognizing hereditary diseases, this study focuses on the use of interpreted features.

Age and gender were assessed using gender.toolpie.com, an online service that showed the best accuracy of age estimates among the libraries tested. Although the images from the database (Dalrymple et al., 2013) have metadata, age and gender recognition in the control group was also carried out automatically for similar processing of the two databases.

After automatic age and gender recognition, those images are selected in which the estimated age is from 6 to 16 years. Z-scores were calculated using statistics from the Facebase project.

Figure 9 shows histograms of the number of feature deviations for Williams syndrome and the norm, where 13 (a, c) and 32 features (b, d) are considered.



a) AUC = 0.898 b) AUC = 0.943

c) AUC = 0.906 d) AUC = 0.954

Figure 9: Separation of Williams syndrome and norm, open database (a and b – the number of deviations for 13 and 32 features, c and d – the sum of the absolute values of z-scores for 13 and 32 features). The norm is indicated in blue; Williams syndrome is indicated in orange.

Similar studies were carried out on images of other syndromes from an open database. Table 3 shows the AUC values for different syndromes and norms. For most syndromes, the best separation is obtained by summing the absolute z-score values of 32 features.

Table 3: Results of the syndrome-norm division (32 only).

Syndrome	Number of face images	Number of features with deviations, AUC	Sum of |z-scores|, AUC
Angelman	83	0.973	0.976
Apert	48	0.920	0.934
Cornelia de Lange	38	0.831	0.829
Down	30	0.957	0.952
fragile X	54	0.893	0.925
Progeria	23	0.850	0.896
Treacher Collins	37	0.724	0.779
Williams	76	0.943	0.954

2.3.2 Own Database

The developed method for assessing phenotypic traits was also tested on a verified database of patients with hereditary diseases provided by Filatov Moscow Pediatric Clinical Hospital.

Figure 10 shows histograms of the number of feature deviations for Williams syndrome and the norm, where 13 (a, c) and 32 features (b, d) are considered. True age and gender data were used for images of Williams syndrome and the norm (17 images – for Williams syndrome, 80 images – for the norm). The age of the patients is from 6 to 16 years.

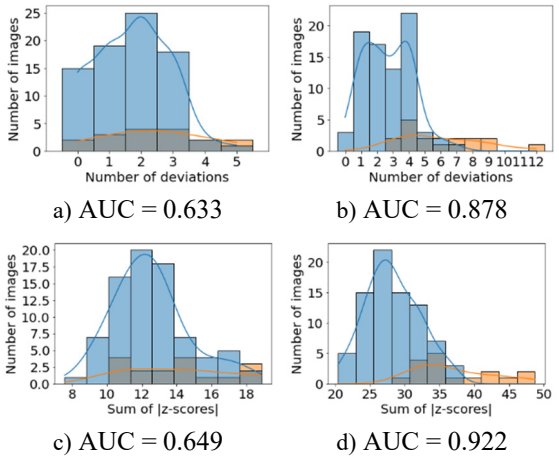


Figure 10: Separation of Williams syndrome and norm, own database (a and b – the number of deviations for 13 and 32 features, c and d – the sum of the absolute values of z-scores for 13 and 32 features). The norm is indicated in blue; Williams syndrome is indicated in orange.

On our database of images of patients with hereditary diseases, the best separation also summates the absolute values of the z-score of 32 traits.

To form risk groups for hereditary syndromes, it is advisable to summarize the absolute values of z-scores of phenotypic traits. For Williams syndrome, this approach provides an AUC value of 0.922 in the studied sample, which is statistically significant (α = 0.01) higher than when using the traditional approach to count the number of features with identified deviations.

3 CONCLUSIONS

A method for recognizing facial phenotypic features from a 2D image has been developed and investigated. The method is based on the detection of the facial points from a reconstructed 3D image and provides recognition of phenotypic features with an accuracy of 84 % to 100 %.

In addition, a criterion for forming a risk group for Williams syndrome was proposed based on the summation of the absolute values of z-scores of phenotypic traits, and a statistically significant increase in the AUC was shown in comparison with the traditional approach to screening by phenotype.

The practical application of the developed method for recognizing phenotypic features will make it possible to significantly supplement the information available in the scientific and medical literature on the values of phenotypic features of the facial area in norm and with the presence of hereditary diseases. Furthermore, these results will increase the reliability of such studies and create a diagnostic decision support system for the physician based on the interpretation of phenotypic traits. In particular, it is possible to create a web service and implement the method in the form of a telemedicine system (Buldakova and Lantsberg, 2019; Buldakova, 2019).

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